39 THE NOVEL POLYPEPTIDE THYMOPOIETIN POTENTLY AND SPECIFICALLY INTERACTS AT THE NICOTINIC α-BUNGAROTOXIN RECEPTOR POPULATION IN NERVOUS TISSUE

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Evidence suggests that there exists at least two populations of nicotinic receptors in nervous tissue. These include the nicotinic acetylcholine receptor (nAchR) which binds monoclonal antibodies against the nicotinic receptor and which also binds [^{3}H]nicotine with high affinity but not α-bungarotoxin (α-BGT). The other site is the α-BGT site, which binds the α-toxin with high affinity and nicotinic receptor ligands with a lower affinity. With regard to function, the nAchR appears to be involved in mediating synaptic events, while the role of the nicotinic α-BGT site in the nervous system is not known. However, the observation that the toxin binds with such specificity and selectivity to a site with the characteristics of a nicotinic receptor, infers that the site is of significance; it may have developed to mediated certain specialized functions related to the nicotinic system.

In addition to the idea that the α-BGT site may mediate functions distinct from those conventionally associated with the nicotinic receptor, it is also possible that the toxin binding site may be the receptor for other ligands, as well as Ach. Recent studies in our laboratory have focused on thymopoietin, a 49 amino acid polypeptide isolated from thymus, which is involved in immune mediated responses. Thymopoietin potently and specifically inhibited [^{125}I]α-BGT binding (IC50 = 3-10 nM) to brain membranes. Nicotinic receptor ligands also inhibited α-BGT binding at uM concentrations, in agreement with previous work. Since thymopoietin has been identified in CNS tissue, these results suggest that the nicotinic α-BGT receptor population in brain can be affected by two distinct classes of agents, the polypeptide thymopoietin and nicotinic receptor ligands.

Studies were done to determine whether thymopoietin could regulate the nicotinic α-BGT receptor population. Chromaffin cells in culture, which are of neural crest origin, were used for this purpose since the α-BGT sites in these cells can readily be altered. Long term exposure (2 to 7 days) of the cells in culture to thymopoietin resulted in an increase in the number of α-BGT sites without affecting receptor affinity. Interestingly, the thymopoietin induced increase in the receptors could be reversed by exposure of the cells to nicotine. This finding suggests that the sites up-regulated by the polypeptide still retain nicotinic characteristics. It thus appears that the α-BGT site not only interacts with, but can also be regulated by, both nicotinic cholinergic ligands and the thymic polypeptide.

Experiments to assess possible functional consequences of thymopoietin in nervous tissue showed that thymopoietin enhanced process formation in a neuronal cell line (PC 12) in culture. These results could suggest that thymopoietin represents a trophic factor for neuronal cells, possibly interacting at the nicotinic α-BGT site. Experiments are currently in progress to determine whether nicotinic receptor ligands modulate the thymopoietin induced neurite extension in the cells in culture.

To conclude, the present work indicates that thymopoietin, as well as nicotinic receptor ligands, may be endogenous ligands for the α-BGT site. Studies to investigate the interaction between nicotine and thymopoietin at the α-toxin binding site in neuronal tissues are currently in progress

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